## Remarks

### *Amendment*

Claims 1-26 are pending. Claims 1, 3, 4, 6, 17, 19, and 23 have been amended. Claim 5 has been canceled. Claim 1 was amended to incorporate the limitations of canceled claim 5 and define the size of the particles as being less than 1 μm in diameter. Support for this amendment can be found in the specification at least at page 67, lines 18-23 and claim 5 as originally filed. Claim 3 was amended to depend from Claim 1. Support for this amendment can be found in the specification at least at page 8, lines 20-22. Claims 4 and 6 were amended to refer to the particle's diameter. Claim 17 was amended to depend from claim 16, as suggested by the examiner. Claim 19 was amended to state that the solvent and non-solvent are slightly miscible. Support for this amendment can be found in the specification at least at page 15, lines 5-6. Claim 23 was amended to clarify the scope of the claim. Support for this amendment can be found in the specification at least at page 7, lines 20-26 and page 4, lines 19-21.

The claims are directed to methods for making dry, micronized particles. Claim 1 defines the method as containing four steps: (1) dissolving a macromolecular material, such as a polymer, in an effective amount of solvent to form a solution, (2) dissolving or dispersing an agent in the solution to form a mixture, which reduces the size of the agent, (3) freezing the mixture, and (4) drying the frozen mixture by vacuum to form solid particles of agent dispersed in a solid macromolecular material. The size of the agent is decreased while it is dissolved or dispersed in solution, prior to the freeze-drying steps. This results in the formation of smaller

drug particles (see page 5, lines 5-9). In the claimed method, the matrix stabilizes and helps maintain the small size of the micronized particles of the agent. The method may also contain a step for separating the micronized particles from the macromolecular matrix (see claim 2). Optionally, the micronized particles of agent and the macromolecular matrix may be microencapsulated in a subsequent step.

**Rejection Under 35 U.S.C. § 112, second paragraph**

Claims 17, 19, and 23 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claim 17 was amended to depend from claim 16, as suggested by the Examiner. Claim 19 has been amended to define the solvent and non-solvent as being slightly miscible. Claim 23 has been amended to more clearly define the scope of the claim, as suggested by the Examiner. Thus the claims as amended are definite.

**Rejection Under 35 U.S.C. § 102**

Claims 1-3, 7-19, and 23-26 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,817,343 to Burke ("Burke"). Claims 1-3, 7-19, and 23-26 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,407,609 to Tice ("Tice"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

***Burke***

Burke discloses a method for forming polymer/drug microparticles by dispersing a solid drug in a polymer solution to form a mixture; removing solvent from the mixture to form a hard matrix containing the drug particles in polymer; and micronizing the matrix by fragmenting (e.g., grinding, milling) the matrix below the glass-transition point of the polymer. Burke requires the step of grinding or milling to micronize the matrix. In contrast, applicants micronize the particles while the agent is dissolved or dispersed in solution with the matrix material. Applicants claimed method allows for the formation of smaller drug particles. In contrast, Burke requires a milling or grinding step to reduce the size of the drug-containing matrix particles. Thus, claims 1-3, 7-19, and 23-26 are novel over Burke.

***Tice***

Tice discloses a microencapsulation process. Tice is not directed to forming small drug particles. In the phase separation microencapsualtion process, Tice teaches that solvent is removed from the microparticles quickly, by solvent evaporation. Tice does not teach nor suggest that the emulsion, containing the polymer and its solvent, the agent to be encapsulated, and a nonsolvent, should be frozen and then placed in a vacuum to remove the solvent. Thus Tice does not disclose every step of the claimed methods. Claims 1-3, 7-19, and 23-26 are novel over Tice.

## Rejection Under 35 U.S.C. § 103

Claims 1-26 were rejected under 35 U.S.C. § 103(a) as being obvious over Burke. Claims 1-26 were rejected under 35 U.S.C. § 103(a) as being obvious over Tice. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

As discussed above, neither Tice nor Burke is directed to the claimed method for micronization. Burke teaches that a matrix which contains a drug must be milled or ground to produce small matrix particles. Tice teaches is process for microencapsulation, not micronization. Further, neither teaches nor suggests the claimed method, which is directed at the formation of drug particles where at least 90% are less than less than 1μm. Neither reference even addresses the size of the drug particles. Thus, the claims as amended are novel in view of Tice and Burke.

Allowance of claims 1-4 and 6-26, as amended, is respectfully solicited.

Respectfully submitted,

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## Certificate of Mailing under 37 C.F.R. § 1.8(a)

I hereby certify that this Amendment and Response, and any documents referred to as attached therein, are being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, U.S. Patent and Trademark Office, Washington, DC 20231.

Aisha Wyatt

Date: September 10, 2002

## Marked Up Version of Amended Claims

## Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A method for making dry, micronized particles of an agent, comprising:

(a) dissolving a macromolecular material in an effective amount of a solvent, to form a solution;

(b) dissolving or dispersing the agent in the solution to form a mixture;

(c) freezing the mixture; and

(d) drying by vacuum the mixture to form solid to form solid micronized particles of the agent dispersed in solid macromolecular material, wherein greater than 90% of the solid particles are less than 1 μm in diameter.

2. The method of claim 1 further comprising separating the solid particles of agent from the solid macromolecular material.

3. (Amended) The method of claim [2] 1 further comprising encapsulating the solid particles of agent in an encapsulating material.

4. (Amended) The method of claim 1 wherein greater than 90% solid particles are less than 0.2 μm in [size] diameter.

Please cancel claim 5.

6. (Amended) The method of claim 1 wherein greater than 90% of the solid particles are between 10 nm and 1 μm in diameter.

7. The method of claim 1 wherein the agent is a bioactive agent.

8. The method of claim 7 wherein the bioactive agent is a protein.

9. The method of claim 8 wherein the protein is a growth hormone.

10. The method of claim 8 wherein the protein is an osteoprotegrenin.

11. The method of claim 7 wherein the agent is selected from the group consisting of peptides, antibiotics, nucleotide molecules, and synthetic drugs.

12. The method of claim 1 wherein the macromolecular material is a polymer.

13. The method of claim 12 wherein the polymer is selected from the group consisting of polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, polyurethanes, poly(butic acid), poly(valeric acid), poly(caprolactone), poly(hydroxybutyrate), poly(lactide-co-glycolide), poly(lactide-co-caprolactone), and blends and copolymers thereof.

14. The method of claim 1 wherein the mixture of step (b) is an emulsion.

15. The method of claim 1 wherein step (d) utilizes lyophilization.

16. The method of claim 3 wherein the encapsulation is conducting using a process selected from the group consisting of interfacial polycondensation, spray drying, hot melt microencapsulation, and phase separation techniques.

17. (Amended) The method of claim [12] <u>16</u> wherein the phase separation technique is selected from the group consisting of solvent extraction, solvent evaporation, and phase inversion.

18. The method of claim 17 wherein the mixture has a continuous phase containing the solvent and wherein the phase inversion technique comprises:

introducing the mixture into a nonsolvent, wherein the volume ratio of solvent:nonsolvent is at least 1:40, to cause the spontaneous formation of a microencapsulated product, wherein the solvent and the nonsolvent are miscible.

19. (Amended) The method of claim 18 wherein [0 less than $\delta$ solvent – $\delta$ nonsolvent less than 6] the solvent and non-solvent are slightly miscible.

20. The method of claim 18 wherein the volume ratio of solvent:nonsolvent is between 1:50 and 1:200.

21. The method of claim 18 wherein the macromolecular material is dissolved in the solvent at a concentration of less than 10% weight per volume and wherein the mixture has a viscosity of less than 3.5 cP.

22. The method of claim 20 wherein the concentration of the macromolecular material in the solvent is between 0.5 and 5% weight per volume.

23. (Amended) The method of claim 8 wherein freezing of the mixture is performed [sufficiently rapidly] following addition of the agent to the solution at a rate effective to avoid [such that] denaturing of the protein [is substantially avoided].

24. The method of claim 2 wherein the particles of agent are separated from the solid macromolecular material using a method comprising

dissolving the macromolecular material in an effective amount of a solvent for the macromolecular material, wherein the solvent is a nonsolvent for the agent.

25. The method of claim 3 wherein the encapsulating material is a biocompatible polymer.

26. The method of claim 25 wherein the biocompatible polymer is selected from polyesters, polyanhydrides, polystyrenes, poly(ortho)esters, copolymers thereof, and blends thereof.